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# TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

| | |
|---|---|
| Total Number of Pages in This Submission | 14 |

| | |
|---|---|
| **Application Number** | 09/464,416 |
| **Filing Date** | 12/16/1999 |
| **First Named Inventor** | Yasmin Thanavala et al. |
| Group Art Unit | 1651 |
| Examiner Name | M. Flood |
| Attorney Docket Number | RPP:156B US |

## ENCLOSURES (*check all that apply*)

- ☒ Fee Transmittal Form
  - ☒ Fee Attached
- ☐ Amendment / Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Assignment Papers (for an Application)
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
- ☐ After Allowance Communication to Group
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☒ Appeal Communication to Group (Appeal Notice, Brief, Reply Brief)
- ☐ Proprietary Information
- ☐ Status Letter
- ☐ Other Enclosure(s) (please identify below):

Remarks

## SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

| | |
|---|---|
| Firm or Individual name | Michael L. Dunn, Dunn & Associates |
| Signature | |
| Date | May 2, 2001 |

## CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231 on this date: May 2, 2001

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| Typed or printed name | Michael L. Dunn | | |
| Signature | | Date | May 2, 2001 |

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# FEE TRANSMITTAL for FY 2001

Patent fees are subject to annual revision.

| TOTAL AMOUNT OF PAYMENT | ($) 155.00 |
|---|---|

| Complete if Known | |
|---|---|
| Application Number | 09/464,416 |
| Filing Date | 12/16/1999 |
| First Named Inventor | Yasmin Thanavala et al |
| Examiner Name | M. Flood |
| Group Art Unit | 1651 |
| Attorney Docket No. | RPP:156B US |



## METHOD OF PAYMENT

1. ☐ The Commissioner is hereby authorized to charge indicated fees and credit any overpayment to:

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☒ Charge Any Additional Fee Required Under 37 CFR 1.16, 1.17, 1.18 and 1.20

☐ Applicant claims small entity status. See 37 CFR 1.27

2. ☒ **Payment Enclosed:**

☒ Check ☐ Credit Card ☐ Money Order ☐ Other

## FEE CALCULATION

### 1. BASIC FILING FEE

| Large Entity Fee Code | Large Entity Fee ($) | Small Entity Fee Code | Small Entity Fee ($) | Fee Description | Fee Paid |
|---|---|---|---|---|---|
| 101 | 710 | 201 | 355 | Utility filing fee | $ |
| 106 | 320 | 206 | 160 | Design filing fee | |
| 107 | 490 | 207 | 245 | Plant filing fee | |
| 108 | 710 | 208 | 355 | Reissue filing fee | |
| 114 | 150 | 214 | 75 | Provisional filing fee | |

SUBTOTAL (1) ($)

### 2. EXTRA CLAIM FEES

| | | Extra Claims | | Fee from below | | Fee Paid |
|---|---|---|---|---|---|---|
| Total Claims | -20** = | | X | | = | |
| Independent Claims | -3** = | | X | | = | |
| Multiple Dependent | | | | | = | |

| Large Entity Fee Code | Large Entity Fee ($) | Small Entity Fee Code | Small Entity Fee ($) | Fee Description |
|---|---|---|---|---|
| 103 | 18 | 203 | 9 | Claims in excess of 20 |
| 102 | 80 | 202 | 40 | Independent claims in excess of 3 |
| 104 | 270 | 204 | 135 | Multiple dependent claim, if not paid |
| 109 | 80 | 209 | 40 | **Reissue independent claims over original patent |
| 110 | 18 | 210 | 9 | **Reissue claims in excess of 20 and over original patent |

SUBTOTAL (2) ($)

**or number previously paid, if greater; For Reissues, see above

## FEE CALCULATION (continued)

### 3. ADDITIONAL FEES

| Large Entity Fee Code | Large Entity Fee ($) | Small Entity Fee Code | Small Entity Fee ($) | Fee Description | Fee Paid |
|---|---|---|---|---|---|
| 105 | 130 | 205 | 65 | Surcharge - late filing fee or oath | |
| 127 | 50 | 227 | 25 | Surcharge - late provisional filing fee or cover sheet | |
| 139 | 130 | 139 | 130 | Non-English specification | |
| 147 | 2,520 | 147 | 2,520 | For filing a request for ex parte reexamination | |
| 112 | 920* | 112 | 920* | Requesting publication of SIR prior to Examiner action | |
| 113 | 1,840* | 113 | 1,840* | Requesting publication of SIR after Examination action | |
| 115 | 110 | 215 | 55 | Extension for reply within first month | |
| 116 | 390 | 216 | 195 | Extension for reply within second month | |
| 117 | 890 | 217 | 445 | Extension for reply within third month | |
| 118 | 1,390 | 218 | 695 | Extension for reply within fourth month | |
| 128 | 1,890 | 228 | 945 | Extension for reply within fifth month | |
| 119 | 310 | 219 | 155 | Notice of Appeal | |
| 120 | 310 | 220 | 155 | Filing a brief in support of an appeal | 155 |
| 121 | 270 | 221 | 135 | Request for oral hearing | |
| 138 | 1,510 | 138 | 1,510 | Petition to institute a public use proceeding | |
| 140 | 110 | 240 | 55 | Petition to revive - unavoidable | |
| 141 | 1,240 | 241 | 620 | Petition to revive - unintentional | |
| 142 | 1,240 | 242 | 620 | Utility issue fee (or reissue) | |
| 143 | 440 | 243 | 220 | Design issue fee | |
| 144 | 600 | 244 | 300 | Plant issue fee | |
| 122 | 130 | 122 | 130 | Petitions to the Commissioner | |
| 123 | 50 | 123 | 50 | Processing fee under 37 CFR 1.17(q) | |
| 126 | 180 | 126 | 180 | Submission of Information Disclosure Stmt | |
| 581 | 40 | 581 | 40 | Recording each patent assignment per property (times number of properties) | |
| 146 | 710 | 246 | 355 | Filing a submission after final rejection (37 CFR § 1.129(a)) | |
| 149 | 710 | 249 | 355 | For each additional invention to be examined (37 CFR § 1.129(b)) | |
| 179 | 710 | 279 | 355 | Request for Continued Examination (RCE) | |
| 169 | 900 | 169 | 900 | Request for expedited examination of a design application | |

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid SUBTOTAL (3) ($) 155.00

## SUBMITTED BY

Complete (if applicable)

| Name (Print/Type) | Michael L. Dunn | Registration No. (Attorney/Agent) | 25,330 | Telephone | 716-433-1661 |
|---|---|---|---|---|---|
| Signature | | | | Date | May 2, 2001 |

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(3)

1093

RPP:156B US

**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**
**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

#16
B.G.J
5/9/01

| | | | |
|---|---|---|---|
| Applicants: | Yasmin Thanavala, et al. | Art Unit: | 1651 |
| Serial No: | 09/464,416 | | |
| Filed: | December 16, 1999 | | |
| Examiner: | M. Flood | | |
| For: | ORAL IMMUNOLOGY USING PLANT PRODUCT CONTAINING A NON-ENTERIC PATHOGEN ANTIGEN | | |

**APPEAL BRIEF**
(37 CFR 1.192)

Box AF
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants respectfully appeal the decision of the Examiner finally rejecting Claims 1-3 and 5-12 set forth in the Office Action dated October 3, 2000. A Notice of Appeal was timely filed by the Applicants on March 5, 2001 (mailed to the U.S. Patent and Trademark Office on March 2, 2001, along with requisite 2 month extension of time).



Real Parties in Interest

The real parties in interest are Health Research, Inc. and Boyce Thompson Institute for Plant Research, Inc., assignees of the entire interest in the patent application.

Related Appeals and Interferences

Parent Application Serial No. 09/420,695, filed October 19, 1999, is currently on appeal.

## Status of Claims

The application originally contained 12 claims. Claim 4 has been canceled. Claims 1, 3 and 11 have been amended. Claims 1-3 and 5-12 are pending on Appeal.

## Status of Amendments

Claims 1, 3 and 11 have been amended. Our amendment filed February 1, 2001, in response to the final Official Action dated October 3, 2000, was not entered because the amendments to the claims raised new issues.

## Summary of the Invention

The invention is a method for providing immune response in a mammal that is specific to an antigen to a non-enteric pathogen (NEPA). The pathogen is a pathogen that invades through a breach in the skin and that does not raise a protective enteric immune response in mammals free of acquired immunity to the pathogen in the absence of an oral adjuvant. The method includes feeding the mammal with a substance comprising a physiologically acceptable material from a plant containing the NEPA, expressed by the plant, in combination with an orally effective adjuvant. The combination causes an immune response to oral administration specific to the NEPA stronger than a response specific to NEPA caused by the NEPA alone.

## Issues Presented for Review

Whether Claims 1-3 and 5-12 are patentable under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Whether Claims 1-3 and 5-12 are patentable under 35 U.S.C. 103(a) over U.S. Patent 5,914,123 to Arntzen et al. in view of U.S. Patent 5,935,570 to Koprowski et al., and further in view of Stites et al., Basic and Clinical Immunology, 7th ed., Appleton & Lange.

Grouping of Claims

The claims do not stand or fall together. For example, Claim 3 gives specific pathogens which would not be obvious in view of a more restrictive pathogen within Claim 1. Further, the subclaims give specific treatment methods that would not necessarily be obvious from a reference broadly suggesting Claim 1.

Argument

Claims 1-3 and 5-12 have been rejected under 35 U.S.C. 112, first paragraph, for lack of enablement. The amendment is based upon the allegation that enablement is not provided for providing an immune response to non-enteric pathogens selected from the group consisting of hepatitis C, hepatitis delta, yellow fever, dengue Homeric fever, tetanus, staphylococcus aureous, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever (listed in claim 3 only). Since the specific NEP's are not listed in Claim 1, to which the rejection applies, the Examiner's argument with respect to Claim 1 is unclear.

In any case the rejection should be withdrawn since there is in fact clear enabling support in the specification.

The Examiner has said on page 7 that "Arntzen teaches methods of making a transgenic plant expressing an immunogen derived from Hepatitis B surface antigen...." and on page 8 "Koprowski also teaches that when the plant containing the NEPA is delivered, it can be

delivered with an adjuvant to facilitate or improve its immunological therapeutic activity." Kaprowski is concerned with viral pathogens in general (see e.g. column 7, lines 18-47) but does not specifically mention hepatitis B. The Examiner states that the teachings of Kaprowski with respect to pathogens in general in combination with Arntzen and Stites make the present results "no more than a combination of known drugs administered by very old an (sic) well known methods in the art..."

It is difficult to reconcile the above statements and allegations of the Examiner with a position that the present application does not provide enablement. Enablement must be considered in light of knowledge available to one skilled in the art, including the teachings of the references cited by the Examiner. This is especially true since a number of prior art documents, including cited Arntzen patent 5,914,123, have been incorporated by reference. Almost the entire Arntzen patent teaches how numerous plants can be genetically transformed to encode foreign genes and specifically teaches incorporation of antigens for poliomyelitis, measles, mumps, rubella, smallpox, yellow fever, hepatitis B, influenza, rabies, adenoviruses, Japanese b encephalitis, varicella, parvovirus, feline leukemia, etc. Similar teachings are given in the other patents incorporated by reference. **There is therefore more than sufficient teaching for making a transgenic plant required for use in accordance with the present invention as broadly as claimed and it is also clearly taught that the antigens made by such plants can function as vaccines when separated from the plant material and injected.**

What is not suggested in the cited art is how to make such transgenic plants orally function as vaccines and that is clearly taught in the present application, i.e. use a potato and an

effective oral adjuvant as clearly taught in the specification. ***The invention is thus clearly enabled.***

Claims 1-3 and 5-12 have been rejected under 35 U.S.C. 103 as being unpatentable over U.S. Patent 5,914,123 to Arntzen et al. (B) in view of U.S. Patent 5,935,570 to Koprowski et al. (A), and further in view of Stites et al., Basic and Clinical Immunology, 7th ed., Appleton & Lange (U).

Arntzen et al. teaches a method for making a transgenic tobacco, tomato or potato that expresses HBsAg.

Notwithstanding the Examiner's assertion, **Arntzen et al. does not teach "methods of making a transgenic plant expressing an immunogen derived from hepatitis B surface antigen, wherein the immunogen is capable of eliciting an immune response in an animal by consumption of the plant material."**

Arntzen et al. pays lip service to raising an immune response by ingestion, but in fact give no examples or teachings for obtaining such a result. **The only actual plant examples in Arntzen et al. relate to tomatoes and tobacco. There is no example of ingestion of either one and certainly no example showing that ingestion of either raises an immune response.** In fact, ingestion of the transgenic tomato does not raise any significant immune response (see the Rule 132 Declaration of Dr. Yasmin Thanavala of record) and certainly tobacco cannot be used for such a purpose because it is toxic. **Since there is no teaching in Arntzen et al. of how oral immunization to HBsAg or anything else might be accomplished using a transgenic plant, and in fact the plants made in the examples do not function orally to raise an**

**immune response, as Arntzen et al. alleges, it is clear that there is insufficient teaching or suggestion in Arntzen et al. to support a rejection of the present claims** whether the reference is considered alone or in combination with the other cited references.

Simply making an unsupported allegation in a reference without a teaching as to how the allegation might be accomplished, is not a sufficient teaching to make a method for accomplishing the desired result obvious to one skilled in the art. Prophetic statements cannot be used to form the basis of a rejection, especially when they are unsupported and not true.

Arntzen et al. itself teaches and recognize that not all antigens would cause an immune response if ingested.

Arntzen et al. says in column 15 beginning at line 27,

"The vaccines are conventionally administered parenterally, by injection, for example either subcutaneously or intramuscularly. Additional formulations which are suitable for other modes of administration include suppositories and, ***in some cases***, oral formulations or aerosols." (emphasis added).

But there is no teaching or suggestion in Arntzen et al. of how the "some cases" could be determined or how the "some cases" could be accomplished.

While Arntzen et al. suggest that tomato juice containing HBsAg might be used as a vaccine, in fact Arntzen provides no supporting data showing any immune response whatsoever to tomato juice or any other plant containing HBsAg. To the extent that Arntzen teaches that tomato juice or any other plant material containing HBsAg can be used as a vaccine, it is an inoperative reference since there is no teaching or suggestion as to how that might be done. ***Simply ingesting the plant material, as suggested by Arntzen et al., does not confer immunity*** at least in the sense that there is a protective response.

There is good reason for Arntzen's omission of data showing a protective immune response to HBsAg by ingesting food material containing it, since prior to the present invention, in fact, there was little if any immune response whatsoever to HBsAg in orally ingested tomato juice or any other plant expressing HBsAg. See the enclosed Rule 132 Declaration of Dr. Thanavala. The response, if any, is clearly insufficient for the purpose of the present invention.

Reference to the examples in the present specification clearly illustrates that priming of the subject of the immunization is required by either pre-vaccination or the use of an effective adjuvant. Arntzen et al. suggests neither. Arntzen et al. doesn't suggest an adjuvant for any purpose whatsoever and certainly does not suggest a combination with an adjuvant that permits the obtaining of a high immune response to orally administered HBsAg as required by the present claims.

Arntzen's suggestion of simple ingestion of plant material expressing HBsAg gives little if any immune response and certainly does not give a sufficient immune response to be considered protective. Arntzen discloses or suggests no way in which a high immune response could be orally obtained.

The Examiner states that Koprowski "teaches methods of making microbially transfected plants expressing a viral antigen which is fed to an animal or human to elicit an immune response." **Koprowski at al. does not teach or suggest any method for making a transgenic plant as required by the present claims** but teaches a microorganism expressing a bioactive compound, e.g. an immunogenic rabies polypeptide. The microorganism may then be used to infect a plant as a parasite but does not alter the genetic character or expression of the plant.

Kaprowski et al. suggest that their method has wide application, e.g. for treatment of viral infections, bacterial infections, fungal infections, protozoan infections, diabetes, immune disorders, cancer and heart disease. Kaprowski et al. more specifically suggest that their method could be used for mucosal pathogens, e.g. rabies, respiratory syncytial virus, cholera. typhoid fever, herpes simplex types I and II, tuberculosis, pathogenic pneumococci, human immunodeficiency virus-1 (HIV-1) and human immunodeficiency virus-2 (HIV-2).

The only specific example given is for rabies which is not considered a nonenteric pathogen in accordance with the present invention since it can invade enterically. There is no enablement for the other suggested applications. If the disclosure actually enabled everything suggested, oral vaccines effective against Aids, cancer, and herpes, among many others, would be made available simply by following the teachings of the Kaprowski et al patent. It is well known that this is not the case.

Kaprowski et al. certainly does not enable or even reasonably suggest application for orally raising an immune response to an antigen by feeding a transgenic plant. The suggestion that an adjuvant be used is a gratuitous statement applied across the entire non-enabled spectrum of the Kaprowski et al. disclosure. There is no suggestion of any specific adjuvant that would have such an effect for purposes of enablement and in fact there is no suggestion that any adjuvant would have any effect whatsoever upon oral immune response to antigens of non-enteric pathogens of the present claims. Adjuvants that can be used in injected vaccines rarely have any significant effect when administered orally.

Stites et al. adds nothing to cure the inadequate teachings and suggestions of Arntzen et al. and Kaprowski et al. Stites et al. does not suggest anything concerning orally raising an immune response to an antigen expressed by a plant. Further, Stites et al. clearly does not suggest any method for **orally** raising a highly effective immune response in the presence of a suitable adjuvant as presently claimed. Adjuvants may "enhance" immune response but in the absence of an immune response to be enhanced, have no effect. Arntzen does not teach any method showing any oral immune response to be enhanced by an adjuvant.

Conclusion

In view of the foregoing, it is clear that the pending claims are patentable over the cited prior art. Reversal of the Examiner and allowance of all claims are therefore respectfully requested.

Respectfully submitted,

Dated: May 2, 2001

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MLD/csc
cc: M. DeLellis
J. Frank

## Appendix

Reprinted below are the claims on appeal:

1. A method for providing immune response in a mammal that is specific to an antigen to a non-enteric pathogen (NEPA), the pathogen being a pathogen that invades through a breach in the skin and that does not raise a protective enteric immune response in mammals free of acquired immunity to the pathogen in the absence of an oral adjuvant, said method comprising feeding the mammal with a substance comprising a physiologically acceptable material from a plant containing the NEPA, expressed by the plant, in combination with an orally effective adjuvant, said combination causing an immune response to oral administration specific to the NEPA stronger than a response specific to NEPA caused by the NEPA alone.

2. The method of Claim 1 where the NEPA is hepatitis B surface antigen (HBsAg).

3. The method of Claim 1 wherein the NEPA is an antigen specific to a non-enteric pathogen selected from the group consisting of those that cause hepatitis B, hepatitis C, hepatitis delta, yellow fever, dengue hemoragic fever, tetanus, staphylococcus aureous, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever.

5. The method of Claim 1 wherein the animal is human.

6. The method of Claim 5 wherein the plant material is from a plant that has been genetically altered to express said antigen.

7. The method of Claim 6 wherein the human ingests sufficient plant material to provide from about 10 to about 100 micrograms of NEPA per kilogram of body weight of the human.

8. The method of Claim 7 wherein the human ingests sufficient plant material to provide from about 2 to about 5 grams of plant material per kilogram of body weight of the human.

9. The method of Claim 8 wherein the human ingests said plant material a plurality of different times, said times being separated from each other by at least 5 days.

10. The method of Claim 9 wherein the plurality of times is three times.

11. The method of Claim 10 wherein the plant material is a material from a plant of the family *Solanaceae*.

12. The method of Claim 11 wherein the plant is a potato.